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EXAMINER	
HUYNH, PHUONG N	

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1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/507,164	CARTLIDGE, SUE ANN	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 April 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-43* is/are pending in the application.

4a) Of the above claim(s) *26-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-25, and 39-41* is/are rejected.

7)☒ Claim(s) *42 and 43* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 15-43 are pending.

2. Claims 26-38 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

3. Claims 15-25, and 39-43 drawn to a probe directed to the KDR/Flk-1 epitope Y1214, the probe is an antibody, a kit comprising said antibody and a method of making said antibody, are being acted upon in this Office Action.

4. In view of the amendment filed 4/4/07, the following rejections remain.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 15-25 and 39-41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) an isolated antibody that detects activation of the KDR/FLK-1 receptor and binds specifically to tyrosine residue Y1214 in KDR receptor (the corresponding tyrosine residue in Flk-1 receptor) wherein the antibody is made by immunizing an animal with a phosphorylated peptide consisting of SEQ ID NO: 1, (2) the said isolated antibody is a monoclonal antibody or a polyclonal antibody, (3) a composition comprising the antibody mentioned above and a carrier, (4) a kit comprising the antibody mentioned above for detecting the activation of the KDR/Flk-1 receptor and reagents for detection assays, (5) a method of generating an isolated antibody that detects activation of the KDR/FLK-1 receptor and binds to tyrosine residue Y1214 in KDR receptor (the corresponding to tyrosine residue in Flk-1 receptor) wherein the method comprises immunizing an animal with a phosphorylated peptide consisting of SEQ ID NO: 1 and isolating the antibody from the animal, (6) a method of generating an isolated antibody that binds to tyrosine residue Y1214 in KDR receptor (the corresponding tyrosine in Flk-1 receptor) wherein the method comprises immunizing an animal with a peptide consisting of SEQ ID NO: 2 and isolating the antibody from the animal, (7) the method of generating antibody

mentioned above wherein the animal is a mammal, (8) the method of generating antibody wherein the peptide consists of any amino acid sequence of KDR/Fl-1, **does not** reasonably provide enablement for (1) any isolated "probe" that detects activation of the KDR/Flk-1 receptor and binds tyrosine residue Y1214 of the KDR/Flk-1 receptor as set forth in claims 15, 19, 20 and 21, (2) any peptide "comprising" Y1214 of the KDR/Flk-1 receptor for a method of generating antibody, (3) any peptide such as peptide "comprising" SEQ ID NO: 2 or peptide "comprising" SEQ ID NO: 1 for a method of generating antibody using such peptide, and (4) any composition or pharmaceutical composition comprising any probe mentioned above. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation. This rejection encompasses three distinct issues, which will be addressed in turn:

Enablement is not commensurate in scope with claims to make and use any "probe" that detects activation of the KDR/Flk-1 receptor and binds tyrosine residue Y1214 of the KDR/Flk-1 receptor.

The specification discloses only monoclonal and polyclonal antibodies that detect activation of the KDR/Flk-1 receptor. The antibody binds specifically to tyrosine residue Y1214 of the KDR receptor (the corresponding SEQ ID NO) and the corresponding tyrosine residue in Flk-1 receptor (the corresponding SEQ ID NO). The specification discloses a phosphorylated peptide consisting of the amino acid sequence of SEQ ID NO: 1 and a non-phosphorylated peptide consisting of SEQ ID NO: 2, see specification page 11. The specification further discloses a method of making antibody using the peptides mentioned above and methods of detecting the activation of the KDR/Flk-1 receptor by measuring the change or level of phosphorylation or the presence or amount of KDR/Flk-1 receptor expressed on a cell in a sample using antibody made with the peptides mentioned above.

The specification does not teach the structure, i.e., nucleotide sequence or peptide sequence or chemical structure of any "probe" that binds to tyrosine residue Y1214 of KDR or the corresponding Y residue in Flk-1 receptor other than antibody. The specification does not teach any assays that are useful for screening probe and is predictive of success in vivo for a pharmaceutical composition. There is not a single nucleotide probe from the smallest to the largest fragment shows any binding specificity and biological effect useful for a medicament for treatment of cancer. Further, there is a lack of in vivo working example demonstrating that the probe is effective for a pharmaceutical composition for the treatment of cancer, see specification page 4, lines 30. Given the unlimited numbers of probes as encompassed by the claims, it is unpredictable which undisclosed nucleotide probe binds specifically to tyrosine residue Y1214 of the KDR, the corresponding residue in Flk-1 receptor, in turn, would be useful for detecting activation of KDR/Flk-1 receptor.

The state of the prior art as exemplified by Wallace et al (in Methods in Enzymology 152: 432-439, 1987; PTO 892) is such that determining the specificity of hybridization probes is empirical by nature and the effect of mismatches within an oligonucleotide probe is unpredictable.

Stryer et al (in Biochemistry, Third edition, W H Freeman Company, New York, pages 31-33, 1998; PTO 892) teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Further, there is a lack of in vivo working example demonstrating any pharmaceutical composition comprising any probe is effective for treating any and all disease. As such, the specification merely extends an invitation to one skilled in the art to further experimentation to arrive at the claimed invention. Since the structure of the probe is not enabled, it follows that any composition or pharmaceutical composition or kit comprising such probe is not enabled.

Enablement is not commensurate in scope with claims to make any antibody that binds specifically to tyrosine residue Y1214 of the KDR/Flk-1 receptor using any peptide "comprising" Y1214 of the KDR receptor or the corresponding tyrosine residue in Flk-1 or any peptide such as peptide comprising SEQ ID NO: 1 or SEQ ID NO: 2 for making antibody.

Even if the probe is limited to antibody such as polyclonal and monoclonal antibody, the specification discloses only two peptides. These peptides consist the amino acid sequence of SEQ ID NO: 1 and SEQ ID NO: 2.

The specification does not teach the structure of any and all peptide "comprising" Y1214 of the KDR/Flk-1 receptor. The specification does not teach immunizing an animal with any peptide other than the peptide consisting of SEQ ID NO: 1 or the peptide consisting of SEQ ID NO: 2 would bind specifically to tyrosine residue Y1214 of the KDR receptor, or the corresponding tyrosine residue in Flk-1 receptor. Even if peptide is limited to SEQ ID NO: 1 and SEQ ID NO: 2, the term "comprising" is open-ended. It expands the peptide of SEQ ID NO: 1 or SEQ ID NO: 2 to include additional amino acids at either or both ends. There is a lack of guidance as to which amino acids to be added such that antibody made with such peptide still binds specifically to Y1214 of the KDR (corresponding SEQ ID NO) and the corresponding tyrosine residue in Flk-1 (corresponding SEQ ID NO).

The state of the prior art as exemplified by Kuby et al (Immunology, Second edition, pages 86-96, 1994; PTO 892) is such that immunizing a peptide may result in **antibody binding specificity** that differs from antibody specificity directed against the native full-length polypeptide. Given the numerous peptides and without the structure, it is unpredictable which antibody generated from which "comprising" SEQ ID NO: 1 or SEQ ID NO: 2 that containing unlimited number of amino acids added will have the same binding specificity as an antibody generated from the specific peptide consisting of SEQ ID NO: 1 or SEQ ID NO: 2, in turn, would bind specifically to the tyrosine residue Y1214 of KDR, or the corresponding residue in Flk-1 for detection assays. As such, the specification merely extends an invitation to one skilled in the art to further experimentation to arrive at the claimed invention. Accordingly, an undue amount of experimentation would be required to determine how to practice the claimed invention. Since the structure of the peptide is not enabled, it follows that any composition or pharmaceutical composition or kit comprising such antibody made with said peptide is not enabled.

Enablement is not commensurate in scope with claims to make and use any pharmaceutical composition comprising any probe, any antibody such as any polyclonal or monoclonal antibody mentioned above. The lack of guidance as to the structure and binding specificity of the probe have been discussed supra. The specification fails to provide any working examples, or guidance with respect to the dosages for a medicament for treatment of cancer.

Zhu et al (Investigational New Drugs 17: 195-212, 1999; PTO 892) teach despite high sequence homology (i.e. 85%) between mouse FLK-1 and its human homolog, KDR, none of the blocking anti-KDR antibodies produced cross-reacts with Flk-1. Consequently, tumors grown in mice, which recruit the mouse vasculature, are not appropriate models to evaluate the anti-

angiogenesis therapy in vivo (see page 201, col. 2, last paragraph, in particular). Given the unlimited numbers of antibody as encompassed by the claims, the lack of in vivo working example, it is unpredictable which antibody made with which undisclosed peptide binds specifically to the tyrosine residue Y1214 of the KDR, or the corresponding residue in Flk-1 receptor for treating any and all cancer.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 4/4/07 have been fully considered but are not found persuasive.

Applicants' position is that antibodies are an example of a probe that can detect activation of KDR/FIk-1 and binds tyrosine residue Y1214 of KDR/FIk-1. Other examples of probes that bind phosphorylation sites of a tyrosine kinase receptor and detect the activation of the receptor are well known in the art. They include binding proteins or binding partners that interact with tyrosine residues. Moreover, antibodies that act as inhibitors of tyrosine kinase receptors activity are well known and some even have been approved by the FDA for treating cancer. For example, Erbitux is a monoclonal antibody that targets epidermal growth factor receptors (see attached Baselga, Eur. J. Cancer, 37:S 16, 2001), and Erbitux has been approved by the FDA for treating colon cancer (see attached UAB Media Relations). Erbitux binds the epidermal growth factor receptors and blocks ligand-induced EGFR phosphorylation. Avastin is another example of a monoclonal antibody that has been approved by the FDA for the treatment of cancer. Avastin has been approved for the treatment of colorectal cancer (see attached FDA News). Also, YcomlD3, a monoclonal antibody against human VEGFR II, has been shown to be efficient in neutralizing VEGF-induced mitogenesis of human endothelial cells (see attached Li et al., Acta Pharmacol Sin. 25(10):1292, 2004). IMC-1C11, an anti-KDR antibody, has been reported to block VEGFR-KDR interaction and inhibit VEGFR-induced endothelial cell proliferation and to be safe and

well tolerated by patients with liver metastases from colorectal carcinoma in a phase I study (see attached Posey et al., Clinical Cancer Research, 9:1323, 2003). Additionally, DC101, an anti-VEGFR-II antibody, has been reported to suppress contact hypersensitivity (see attached Watanabe et al., Experimental Dermatology 13:671, 2004). Thus, antibodies have been shown to be effective as pharmaceutical agents for in vivo use and for the treatment of diseases.

The Office Action alleges that the specification does not teach the chemical structure of any probe and does not provide assays that are useful for obtaining such a probe. Additionally, the Office Action alleges that the claims do not teach all peptides "comprising" Y 1214 of the KDR/Flk-1 for generating the claimed probes. As discussed above, the specification provides antibody as an example of the claimed invention. The specification provides methods for generating antibodies that bind tyrosine residue Y1214 of KDR/Flk-1 and detect activation of KDR/Flk-1 and assays for detecting whether the antibodies bind KDR/Flk-1 and whether the antibodies inhibit KDR/Flk-1 activity. These methods and assays are also well-known to a person of ordinary skill in the art. Moreover, as discussed on page 5, lines 18- 31, assays that are useful for detecting or measuring a change in the activation state of KDR/Flk-1 include fluorimetric assays, chromogenic assays, radiolabelling assays, and chemiluminescence assays which are routinely used by a person of ordinary skill in the art. Takahashi also discloses assays for detecting activation of KDR/Flk-1.

Further, the claims require that the probes not only bind tyrosine residue Y1214 of KDR/Flk-1 but also detect activation of KDR/Flk-1. Thus, the claims are not directed to any probe but only those that bind tyrosine residue Y 1214 of KDR/Flk-1 and detect activation of KDR/Flk-1. Given that assays for determining whether a probe binds the Y 1214 of KDR/Flk-1 and whether a probe can detect the activation of KDR/Flk-1 are well known and described by the specification, one would be able to obtain the probes encompassed by the claims and the peptides comprising SEQ ID NO: 1 or 2 useful for generating antibodies encompassed by the claims. Thus, the specification enables one of ordinary skill in the art to obtain such probe without undue experimentation. Additionally, anti-phosphotyrosine antibodies are known in the art. Some representative examples of such antibodies include 4G10 (see page fig. 2 of Ganju et al., J. of Virology, 72(7): 6131, 1998), 5E2 (see fig. 2 of Redemann et al., Mol. and Cell. Biology, 12(2): 491, 1992), and PY20 (see fig. 2 of Prochazka et al. Biology of Reproduction, 68:797, 2003). Given that there is guidance in the prior art and in the specification for obtaining anti-phosphotyrosine antibodies, it would not require undue experimentation to obtain peptides

comprising SEQ ID NO: 1 or 2 for generating antibodies that bind the Y1214 residue of KDR/Flk-1. It is within the skill of the artisan to obtain peptides comprising SEQ ID NO: 1 or 2 useful for generating an antibody that binds the Y1214 residue of KDR/Flk-1 and to determine whether an antibody generated by such peptide can bind the Y1214 residue of KDR/FIk-1 and detect the activation of KDR/Flk-1, given the assays provided by the specification. Moreover, given the guidance provided by the specification and the prior art, it is within the skill of the artisan to obtain antibodies generated from peptides comprising SEQ ID NO: 1 or 2. Also, it would not require undue experimentation to determine whether antibodies generated from peptides comprising SEQ ID NO: 1 or 2 are able to bind the ¥1214 residue on KDR/FIk-1 because it would be routine to test for the binding of such antibodies to the Y1214 residue on KDR/FIk-1 given the assays provided in the specification. Furthermore, Applicants respectfully assert that given the guidance provided by the specification and what is known in the prior art, it would only require routine experimentation to obtain the probes or the peptides for generating antibodies encompassed by the claims. It is well settled that routine experimentation should not be considered as undue in an enablement assessment.

In response, the issue here is whether the "probe" other than antibody that binds to the phosphorylated tyrosine Y1214 of VEGF receptor KDR is enabled. The specification as filed does not teach any "probe" other than antibody that binds to the phosphorylated tyrosine residue at position 1214 of KDR. The cited various references about antibodies such as Erbitux, IMC-1C11, Avastin and DC101 that bind to receptor and approved by the FDA for treatment of cancer are irrelevant to the claimed invention. In fact, Erbitux binds to a completely different receptor (EGFR), while the claims 16-18 which are not under rejection are drawn to antibody that binds to a VEGF receptor such as KDR/Flk-1 at the phosphorylated tyrosine residue 1214 of KDR. The "probe" as known in the art is DNA probe or RNA probe that binds to nucleic acid sequence. The art does not teach any DNA probe or RNA probe that binds to protein, much less phosphorylated tyrosine residue at position 1214 of KDR/Flk-1. Further, the tyrosine residue for the mouse receptor Flk-1 is not at position 1214 as evidenced by the teachings of Terman et al disclosed at page 9, lines 25-30 of the specification. This is because the mouse Flk-1 has a much longer sequence than the human KDR and the Y residue is located at a completely different position, see sequences in Terman et al reference. Even if the probe is limited to antibody that binds to tyrosine at position 1214 of KDR, the tyrosine residue 1214 is located intracellularly. There is a lack of guidance of any such antibody that penetrates the cell membrane and binds to

Y1214 of KDR expressed on the endothelial cell and inhibits KDR activation for the claimed pharmaceutical composition. This is because the antibody must get *inside* the cell, in order to inhibit KDR activation for treating cancer. Pharmaceutical composition for treating cancer without in vivo working example is unpredictable. Note, all the antibodies cited by applicant, which approved by FDA, bind to extracellular domain of the KDR receptor. With respect to claim 41, the specification does not adequate teach any peptide other than SEQ ID NO: 1 and 2 "consists of any amino acid sequence of KDR/Flk-1" without the amino acid sequence. Accordingly, it would require undue experimentation of one skilled in the art to practice the claimed invention.

7. Claims 15-25 and 39-41 are under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) any isolated "probe" that detects activation of the KDR/Flk-1 receptor and binds tyrosine residue Y1214 of the KDR/Flk-1 receptor as set forth in claims 15, 19, 20 and 21, (2) any peptide "comprising" Y1214 of the KDR/Flk-1 receptor for a method of generating antibody, (3) any peptide such as peptide "comprising" SEQ ID NO: 2 or peptide "comprising" SEQ ID NO: 1 for a method of generating antibody and method of using antibody generated from such peptide for detecting the activation of such KDR/Flk-1 receptor and (4) any "peptide consists of any amino acid sequence of KDR/Flt-1" for the claimed method.

The specification discloses only monoclonal and polyclonal antibodies that detect activation of the KDR/Flk-1 receptor. The antibody binds specifically to tyrosine residue Y1214 of the KDR receptor (the corresponding SEQ ID NO) and the corresponding tyrosine residue in Flk-1 receptor (the corresponding SEQ ID NO). The specification discloses a phosphorylated peptide consisting of the amino acid sequence of SEQ ID NO: 1 and a non-phosphorylated peptide consisting of SEQ ID NO: 2, see specification page 11. The specification further discloses a method of making antibody using the peptides mentioned above and methods of detecting the activation of the KDR/Flk-1 receptor by measuring the change or level of phosphorylation or the presence or amount of KDR/Flk-1 receptor expressed on a cell in a sample using antibody made with the peptides mentioned above.

The specification does not disclose the structure of any "probe" that binds to tyrosine residue Y1214 of KDR or the corresponding Y residue in Flk-1 receptor. A probe without the nucleotide sequence or chemical structure has no structure, much less function. Other than the described antibody mentioned above, the present specification fails to disclose any other probe, let alone a representative number. Since the probe is not adequately described, it follows that a composition or pharmaceutical composition or kit comprising said probe is not adequately described.

With respect to peptide "comprising" Y1214 of the KDR/Flk-1 or peptide "comprising" SEQ ID NO: 1 or SEQ ID NO: 2 for making antibody, the specification discloses only two peptides. These peptides consist the amino acid sequence of SEQ ID NO: 1 and SEQ ID NO: 2. The term "comprising" is open-ended. It expands the peptide Y1214 of the KDR or the tyrosine in the corresponding Flk-1 receptor to include additional amino acids at either or both ends. The specification does not disclose which amino acids to be added, let alone antibody generated with such undisclosed peptide still maintains its binding specificity to tyrosine residue Y1214 of the KDR/Flk-1 receptor. Likewise, a peptide "comprising" SEQ ID NO: 1 or SEQ ID NO: 2 include additional amino acids at either or both ends of SEQ ID NO: 1 and SEQ ID NO: 2. There is a lack of a written description about the amino acids to be added. Further, the specification does not disclose the structure of any other peptide longer than SEQ ID NO: 1 and 2 or any peptide consists of any amino acid sequence of KDR/Flk-1 other than the peptide of SEQ ID NO: 1 and 2. The term "an amino acid sequence of KDR/Flk-1 could be any fragment as little as one amino acid in length. The rejection of claim 41 could be obviate by amending the claim to recite the method ... wherein the peptide consists of the amino acid sequence of KDR/Flk-1. As such, the method of generating antibody using such undisclosed peptide is not adequately described.

The specification discloses only antibody that binds to tyrosine residue at position 1214 (Y1214) of KDR or the corresponding tyrosine residue in Flk-1, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of "probe" to describe the genus for the claimed product. Other than the two specific peptides mentioned above, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of peptide and antibody made with such peptide to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 4/4/07 have been fully considered but are not found persuasive.

Applicants' position is that claims 15-25 as they stand are directed to an isolated probe that detects activation of KDR/Flk-1 and binds tyrosine residue Y1214 of the KDR/Flk-1. The claims recite both structural and functional features to describe the claimed probe. The claims by requiring the probe to bind tyrosine residue Y1214 of KDR/Flk-1 and to detect activation of KDR/FIk-1 provide a structure and function for the probe. The probe must have a certain structure to bind tyrosine residue Y1214 of KDR/Flk-1. The function of the probe is to detect activation of KDR/Flk- 1. The Office Action also alleges that the term "peptide comprising" is "open-ended" encompassing various peptides and that the specification fails to provide a representative number of species of "probe." The Office Action cites University of California v. Eli Lilly and University of Rochester v. G.D. Searle. However, in contrast to the claims in the cited cases, the claims of the present application require that the probe bind tyrosine residue Y 1214 of KDR/Flk-1 and detect activation of KDR/FIk-1. Thus, the claims are not directed to a broad genus of probes. Moreover, the MPEP 2163 states that disclosure of any combination of identifying characteristics that distinguish the claimed invention from other materials would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient and that an inventor is not required to describe every detail of his invention because an applicant's disclosure obligation varies according to the art to which the invention pertains. In the present case, the claims recite identifying characteristics such as binding to Y 1214 of KDR/FIk-1 and detect activation of KDR/FIk-1. The inventors discovered that Y 1124 plays a role in signal transduction from KDR/Flk-1 to the MAP kinase pathway and in the DNA synthesis in endothelial cells. Further, the claims are not directed to peptides comprising Y 1214 of KDR/FIk-1. These peptides are used to generate antibodies that bind Y1214 of KDR/Flk-1 and detect activation of KDR/FLK-1. The claims are directed antibodies that bind Y1214 of KDR/FIk-1 and detect activation of KDR/Flk-1, to methods of generating such antibodies, and to methods of using such antibodies. KDR/Flk-1 is a known tyrosine kinase receptor. The nucleic acid encoding KDR/Flk-1 has been isolated and its amino acid sequence has been determined. Although prior to the present discovery it was not known which tyrosine residue on KDR/Flk-1 is

involved in the activation of the receptor, the structure and function of KDR/Flk-1 was known. Accordingly, the specification provides adequate description of the claimed invention.

In response, the "probe" encompasses deoxyribose and ribonucleic acid sequences as well as any protein that binds to Y1214 of KDR. The "probe" without the amino acid sequence or nucleic acid sequence has no structure, much less function. The specification discloses only antibody that binds to phosphorylated tyrosine residue Y1214 of KDR wherein detection of phosphorylated tyrosine as opposed to unphosphorylated tyrosine indicated that the receptor is activated. The specification does not teach any nucleic acid "probe" as broadly as claimed that detects activation of protein such as KDR/Flk-1, nor does it demonstrate that the probe binds to *protein* on the phosphorylated tyrosine residue Y1214 of KDR/Flk-1. As such, the specification merely extends an invitation to one of ordinary skilled in the art to come up with the structure of the "probe" for the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.).

Adequate written description requires more than a mere statement that it is part of the invention. The amino acid sequence or nucleic acid sequence for probe itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision. (See page 1115.)

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

9. Claims 15-25, and 39-41 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "Y1214 of the KDR/**Flk-1**" in claims 15 and 22 is ambiguous and indefinite because "Y1214" does NOT correspond to the tyrosine residue located at position 1214 in the amino acid sequence of the **mature Flk-1** and the corresponding SEQ ID NO, see reference sequences set out in the Terman et al reference disclosed at page 9, lines 25-30 of the specification. This is because the tyrosine residue "Y1214" at position 1214 is referred to the human KDR and not the mouse Flk-1 set out in the Terman et al reference disclosed at page 9, lines 25-30 of the specification. In fact, the mouse Flk-1 has a much longer sequence than the human KDR and the Y residue is located at a completely different position. As such, one of ordinary skill in the art cannot appraise the metes and bound of the claimed invention.

Applicants' arguments filed 4/4/07 have been fully considered but are not found persuasive.

Applicants' position is that as explained on page 9, lines 25-30 of the specification, the Terman et al. reference discloses that the tyrosine residue at position 1215 instead of 1214 because the sequence begins with an initiator methionine. It is clear that the tyrosine residue is at position 1214 when the initiator methionine is not present, as evidenced by Takahashi (Embo Journal, 2001, 20(11):2768). A quick internet search on Google also indicates that tyrosine at position 1214 on KDR/Flk-1 is well known (see attached search results from Google). Thus, claims 15-25 are not indefinite.

In response, even if the initiator methionine is not present, the tyrosine residue "Y" at position 1214 still does not correspond to the mouse receptor FLK-1. This is because the tyrosine residue "Y1214" at position 1214 is referred to the human KDR and not the mouse Flk-1 set out in the Terman et al reference disclosed at page 9, lines 25-30 of the specification. In fact, the mouse Flk-1 disclosed in the Terman et al reference is a much longer sequence than the human KDR and the Y residue is located at a completely different position. As such, one of ordinary skill in the art cannot appraise the metes and bound of the claimed invention.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 15-20 and 22-25 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Takahashi et al (of record, EMBO J 20(11): 2768-2778, June 2001; PTO 892) in view of Harlow *et al* (in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 139-153).

Takahashi et al teach a method of making a probe such as polyclonal antibody that detects activation of KDR/Flk-1 receptor by VEGF-A and binds tyrosine residue Y1175 of the KDR/Flk-1 receptor. The reference method comprises immunizing an animal such as a rabbit with a peptide such as VCDPDKFHYDNTAG surrounding phosphorylated Y1175 and isolating antibody from the animal (see page 2776, col. 1, Rabbit anti-phosphoY1775 polyclonal antibody, in particular). Takahashi et al also teach tyrosine residues (Y) at position 1175 (Y1175) and **(Y1214)** of the KDR/Flk-1 receptor are the two major VEGF-A dependent autophosphorylation sites in vitro and in vivo (see abstract, page 2770, col. 1, first paragraph, in particular). Takahashi et al also teach phosphorylation of Y1175 is via MAP kinase (see page 2771 col. 1, in particular) but phosphorylation of Y1214 is not, suggesting that tyrosine phosphorylation of Y1214 may be important for other signaling pathways of VEGF-A in endothelial cells such as the stimulation of chemotaxis, cell survival, or the regulation of gene expression (see page 2775, in particular). Takahashi et al further teach peptide such as VCDPKFHYDNTAG surrounding the Y1214 (see page 2769, col. 2, Figure 1, in particular) and providing motivation to the skilled artisan to make antibody using phosphospecific peptide surrounding the tyrosine residue of interest to make antibody that is highly specific and distinguishable from other tyrosine residue and kinase receptors (see page 2774, col. 2, in particular). Takahashi et al teach antibody to phosphotyrosine (anti-PY) is useful for detection of activated KDR/Flk-1, not only in the western blotting but also in histological sections (see paragraph bridging page 2771 and 2772, in particular) and potentially for use alone or in combination with a KDR/Flk-1 tyrosine kinase inhibitor (see page2774, col. 2, in particular). Takahashi et al also teach carrier such as phosphate-buffered saline (PBS) and composition comprising anti-BrdU and PBS (see page 2776, col. 2, Immunocytochemistry, page 2777, col. 1, first paragraph, in particular). Although Takahashi et al does not teach the specific antibody to Y1214 of the KDR/Flk-1 receptor, Takahashi et al do in fact teach epitope surrounding Y1214 such as peptide VCDPKFHYDNTAG, which is nearly identical to the

claimed phosphorylated peptide of SEQ ID NO: 1 (VCDPKFHYDNTAGS) and unphosphorylated peptide of SEQ ID NO: 2 (VCDPKFHYDNTAGS). Clearly, one having ordinary skill in the art would have been motivated with the expectation of success from the teachings of Takahashi et al to make antibody such as polyclonal antibody that is highly specific to Y1214 of KDR/Flk-1 by substituting the peptide VCDPDKFHYDNTAG surrounding PY1175 as immunogen for the other peptide VCDPKFHYDNTAG surrounding PY1214 as taught by Takahashi et al, then immunizing an animal with said peptide and isolating the antibody from the animal.

The invention in claim 17 differs from the teachings of the reference only in that the antibody is a monoclonal antibody instead of polyclonal antibody.

Harlow et al teach a method of making monoclonal antibody to any antigen of interest. Harlow et al further teach the advantages of monoclonal antibody are that the source of antibody will be unlimited, their binding specificity and their homogeneity (see page 141, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make monoclonal antibody as taught by the Harlow et al using the phosphopeptide VCDPKFHYDNTAG surrounding PY1214 as immunogen as taught by Takahashi et al to produce a monoclonal antibody that detects activation of the KDR/Flk-1 receptor and binds specifically to phosphorylated tyrosine residue Y1214 of the KDR receptor (the corresponding Y residue in Flk-1 receptor). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Harlow et al teach the advantages of monoclonal antibody are that the source of antibody will be unlimited, their binding specificity and their homogeneity (see page 141, in particular). Takahashi et al teach tyrosine residues (Y) at position 1214 (Y1214) of the KDR/Flk-1 receptor is one of the two major VEGF-A dependent autophosphorylation sites in vitro and in vivo and phosphospecific peptide such as VCDPKFHYDNTAG surrounding PY1214 is useful for making antibody that is highly specific and distinguishable from other tyrosine residue and kinase receptors (see page 2774, col. 2, in particular). Takahashi et al teach antibody to phosphotyrosine (anti-PY) is useful for detection of activated KDR/Flk-1, not only in the western blotting but also in histological sections (see paragraph bridging page 2771 and 2772, in particular) and potentially for use alone or in combination with a KDR/Flk-1 tyrosine kinase inhibitor (see page2774, col. 2,

in particular). Once the antigen of interest is selected, the use of that antigen in the known method of Kohler and Milstein will result in the expected hybrid cell lines and the specific monoclonal antibodies. Ex parte Erlich, 3 USPQ2d 1011, 1015 (BPAI 1986). Claims 19-20 are included in this rejection because it would have been obvious to one of ordinary skill in the art at the time the invention was made with the expectation of success to substitute the anti-BrdU in a composition comprising and anti-BrdU and PBS for the polyclonal antibody that binds specifically to PY1214 of KDR/Flk-1 for detection of activation of KDR/Flt-1 receptor as taught by Takahashi et al.

Applicants' arguments filed 4/4/07 have been fully considered but are not found persuasive.

Applicants' position is that Takahashi teaches that Y1175, but not Y 1214, plays a crucial role in the transduction of signals to the MAP kinase pathway and DNA synthesis of endothelial cells (page 2769, left column, first paragraph). Thus, Applicants respectfully point out that Takahashi teaches away from obtaining a probe that binds the Y1214 site on KDR/FIk-1 for detecting activation of KDR/FIk-1. Takahashi specifically states on page 2775, "whether tyrosine phosphorylation of Y 1214 is important for other signal pathways of VEGF-1 in endothelial cells, such as the stimulation of chemotaxis, cell survival, or the regulation of gene expression remains to be elucidated." Thus, Takahashi does not teach or suggest that tyrosine phosphorylation of Y 1214 is important for other signal pathways. Rather, the experimental results of Takahashi indicate that Y 1214 on KDR/Flk- 1 is not involved in the transduction of signals to the MAP kinase pathway and in DNA synthesis in endothelial cells. The Office Action also alleges that given the teachings of Takahashi, one would have the motivation to make the claimed probe. Applicants point out that the claims as they stand are directed to a probe that not only binds tyrosine residue Y 1214 of KDR/Flk-1, but also detects activation ofKDR/Flk-1. Moreover, prior to Takahashi's work, it was known that KDR/Flk-1 utilizes the MAP kinase pathway as the major signaling pathway and that tyrosine residues on KDR/Flk-1 are autophosphorylated in response to VEGF-A. Thus, Takahashi performed experiments to better understand the signal transduction mechanism of KDR/Flk- 1 and discovered that Y 1214 of KDR/Flk-1 was not involved in the transduction of signals to the MAP kinase pathway. Accordingly, given the results obtained by Takahashi, one would not have been motivated to obtain a probe that that binds tyrosine residue Y 1214 for detecting activation of KDR/Flk- 1, since activation of KDR/Flk- 1 does not involve the phosphorylation of tyrosine residue Y 1214.

Harlow discloses methods of producing antibodies to any antigen of interest. However, Harlow does not cure the deficiencies of Takashi. Harlow neither teaches a probe that binds the tyrosine residue Y 1214 of KDR/Flk- 1 and detects activation of KDR/Flk- 1 nor provides the motivation for obtaining such a probe. Accordingly, neither the combination of the cited references nor each of the references individually renders the claimed invention obvious.

In response, as applicant pointed out prior to Takahashi's work, it *was known* that KDR/Flk-1 utilizes the MAP kinase pathway as the major signaling pathway and that *tyrosine* residues on KDR/Flk-1 are autophosphorylated in response to VEGF-A. Takahashi et al teach a method of making a probe such as polyclonal antibody that detects activation of KDR/Flk-1 receptor by VEGF-A and binds tyrosine residue Y1175 of the KDR/Flk-1 receptor. The reference method comprises immunizing an animal such as a rabbit with a peptide such as VCDPDKFHYDNTAG surrounding phosphorylated Y1175 and isolating antibody from the animal (see page 2776, col. 1, Rabbit anti-phosphoY1775 polyclonal antibody, in particular). Takahashi et al also teach tyrosine residues (Y) at position **(Y1214)** of the KDR/Flk-1 receptor and *Y1175 and Y1214 are the two major VEGF-A dependent autophosphorylation sites in vitro and in vivo* (see abstract, page 2770, col. 1, first paragraph, in particular). Although Takahashi et al does not make the specific antibody to Y1214 of the KDR/Flk-1 receptor, Takahashi et al do in fact teach epitope surrounding Y1214 such as peptide VCDPKFHYDNTAG, which is deemed to be important in tyrosine phosphorylation and the reference peptide is 100% identical to the claimed phosphorylated peptide of SEQ ID NO: 1 and unphosphorylated peptide of SEQ ID NO: 2. Clearly, one having ordinary skill in the art would have been motivated with the expectation of success from the teachings of Takahashi et al to make antibody such as polyclonal antibody that is highly specific to Y1214 of KDR/Flk-1 by substituting the peptide VCDPDKFHYDNTAG surrounding PY1175 as immunogen for the other peptide VCDPKFHYDNTAG surrounding PY1214 as taught by Takahashi et al, then immunizing an animal with said peptide and isolating the antibody from the animal as taught by Harlow discloses. The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983) see MPEP 2144.

12. Claim 21 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Takahashi et al (of record, EMBO J 20(11): 2768-2778, June 2001; PTO 892) in view of Harlow *et al* (in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 139-153) as applied to claims 15-20 and 22-25 mentioned above and further in view of US 6,204,011 (filed June 17, 1998; PTO 892).

The combined teachings of Takahashi et al and Harlow et al have been discussed supra.

The invention in claim 21 differs from the teachings of the references only in that a kit for comprising a probe that detects activation of the KDR/Flt-1 receptor and binds tyrosine residue Y1214 of the KDR/Flk-1 receptor.

The '011 patent teaches a kit comprising antibodies that bind to human KDR and all the essential reagents required to perform various assays such as detection assays specific for commercial expedience (see col. 21, lines 65-66, col. 22, lines 5-12, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the antibody that binds to KDR in the kit as taught by the '011 patent for the polyclonal antibody that binds to Y1214 of the activated KDR/Flk-1 receptor as taught by Takahashi et al or the monoclonal antibody that binds to Y1214 of the activated KDR/Flk-1 receptor as taught by Takashashi and Harlow et al. A kit will allow for ease of use for the practitioner since all the essential reagents, and standard for use are included in a kit as taught by the '011 patent (see col. 15, lines 54-61, in particular). From the teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Applicants' arguments filed 4/4/07 have been fully considered but are not found persuasive.

Applicants' position is that the deficiencies of Takahashi and Harlow are discussed above. U.S. Patent '011 does not cure the deficiencies of Takahashi and Harlow. U.S. Patent '011 is relied upon for teaching a kit comprising a human KDR protein. However, U.S. Patent '011 neither teaches a probe that binds tyrosine residue Y1214 of KDR/Flk-1 and detects activation of KDR/Flk-1 nor provides the motivation for obtaining such a probe. Accordingly, the cited references do not render the claimed invention obvious.

In response, the motivation to combine the teaching of Takahashi and Harlow has been discussed above.

The invention in claim 21 differs from the teachings of the references only in that a kit for comprising a probe that detects activation of the KDR/Flt-1 receptor and binds tyrosine residue Y1214 of the KDR/Flk-1 receptor.

The '011 patent teaches a kit comprising antibodies that bind to human KDR and all the essential reagents required to perform various assays such as detection assays specific for commercial expedience (see col. 21, lines 65-66, col. 22, lines 5-12, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the antibody that binds to KDR in the kit as taught by the '011 patent for the polyclonal antibody that binds to Y1214 of the activated KDR/Flk-1 receptor as taught by Takahashi et al or the monoclonal antibody that binds to Y1214 of the activated KDR/Flk-1 receptor as taught by Takashashi and Harlow et al. A kit will allow for ease of use for the practitioner since all the essential reagents, and standard for use are included in a kit as taught by the '011 patent (see col. 15, lines 54-61, in particular). From the teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

13. Claims 42-43 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

14. No claim is allowed.

15. **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

17. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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